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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,106	12/23/2004	Shinji Nakade	Q85523	9516

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,106	NAKADE ET AL.	
	Examiner	Art Unit	
	Christina Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 9-20* is/are pending in the application.

4a) Of the above claim(s) *13 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9-12,14-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group III, claims 14 and 20, in the reply filed on 08/28/2006 is acknowledged. Upon further consideration, claims 12 and 18 (formerly of Group I) are grouped with the elected claims because formulas I and III are not patentably distinct. The election of the species (4'-{[(3-phenylpropyl)(3,4,5-trimethoxybenzoyl)amino]methyl}-2-biphenyl)acetic acid without traverse is also acknowledged. Claims 7 and 9-20 are pending; claims 13 and 19 are withdrawn from consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 7 and 9-12, 14-18, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

4. Claims 7, 9, 10, 11 and 15-17 are drawn to methods and compositions involving EDG-2 antagonists. Claims 12 and 18, and 14 and 20 are drawn to EDG-2 antagonists of Formulas I and III, respectively. The specification discloses the complete structure of compounds 1-48, species of formulas I and III. Of these 48 compounds only 3-(N-((2-(2-((pyridin-3-ylmethylamino)carbonyl)phenyl)phenyl)carbonyl)-N-(2-(2,5-dimethoxyphenyl)ethyl)amino)propanoic acid hydrochloride (compound a or 7) and (4'-{[(3-phenylpropyl)(3,4,5-trimethoxybenzoyl)amino]methyl}-2-biphenyl)acetic acid (compound c or 37) are shown to have EDG-2 antagonist activity. The specification does not provide a description of the physical and chemical properties that distinguish EDG-2 antagonists, or guidance on how to obtain additional species of formulas I and III or any other type of compound that are EDG-2 antagonists. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

5. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

6. Therefore, only compounds 1-48, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath*

makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claims 7 and 9-12, 14-18, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

8. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) the nature of the invention

9. Claims 7, 9, 10, 11 and 15-17 are drawn to methods and compositions involving EDG-2 antagonists. Claims 12 and 18, and 14 and 20 are drawn to EDG-2 antagonists of Formulas I and III, respectively. The methods and compositions are designed for the treatment of chronic diseases, prostate hyperplasia in particular.

(2) the state of the prior art

10. Lysophosphatidic acid is a simple bioactive phospholipid (Contos *et al.*, *Mol. Pharm.*, **2000**, *58*, 1188). It acts through specific G-protein-coupled receptors and has proliferative and/or

morphological effects on many cell types. EDG-2 is one of the eight known mammalian LPA receptors. The physiological role of this receptor is only beginning to be explored. Pages *et al.* (*J. Biol. Chem.*, **2001**, *276*, 11599) report a specific role for this receptor in the LPA-dependent control of preadipocyte proliferation and spreading. Shankar *et al.* (U.S. Publication No. 2004/0167132) teach pharmaceutical compositions comprising EDG-2 antagonists (see abstract). Shankar *et al.* do not provide methods for treating chronic diseases with these compositions. Adolfsson *et al.* (*Prost.*, **2002**, *51*, 50) report that LPA stimulates the proliferation of cultured smooth muscle cells from human benign prostate hyperplasia tissue but do not report the specific receptor related to this activity.

(3) the relative skill of those in the art

11. The relative skill of those in the art is high.

(4) the predictability or unpredictability of the art

12. The role of the EDG-2 receptor in chronic disease has not been established.

13. There is no method known in the art that can prevent all chronic diseases.

14. Medicinal treatments for benign prostate hyperplasia are known to be effective at managing this disease (Vacherot *et al.*, *Prost.*, **2000**, *45*, 259).

15. Obesity is a serious chronic disease that must be treated by weight loss. Weight loss is difficult to maintain. Most protocols for successful weight management involve lifestyle changes such as diet and exercise however a limited number of medicines for long term appetite suppression are available (Dixon, *Austr. Fam. Phys.*, **2006**, *35*, 576).

16. Rheumatoid arthritis is a chronic inflammatory disease that cannot be cured however several medications are available to treat and manage the disease (Rindfleisch *et al.*, *Am. Fam. Phys.*, **2005**, *72*, 1037).

(5) the breadth of the claims

17. All chronic diseases are included in the scope of claims 7, 9, 12, 14, 15, 18 and 20. EDG-2 antagonist of all chemical forms are included in the scope of claims 7, 9-11, and 15-17. Claims 14 and 20, drawn to formula III, are extremely broad as formula III lacks a core chemical structure. Formula I, a subgenus of formula III, has defined core structure but includes many broadly defined variable groups.

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples

18. Despite the breadth of the claims, the specification provides only limited working examples. Only 3-(N-((2-(2-((pyridin-3-ylmethylamino)carbonyl)phenyl)phenyl)carbonyl)-N-(2-(2,5-dimethoxyphenyl)ethyl)amino)propanoic acid hydrochloride (compound a or 7) and (4'-{[(3-phenylpropyl)(3,4,5-trimethoxybenzoyl)amino]methyl}-2-biphenyl)acetic acid (compound c or 37) are shown to have EDG-2 antagonist activity.

19. Both compounds suppress the proliferative effect of LPA on normal human prostate stroma cells. Vacherot *et al.* (*Prost.*, **2000**, *45*, 259) report that Permixon, a known therapy for prostate hyperplasia, functions by inhibiting the proliferation of prostate stroma cells. It is not clear whether or not this *in vitro* activity is predictive of *in vivo* efficacy at treating the disease. It is not known, for example, how the inhibitory effect of compounds a and c compares to that of Permixon. Furthermore, Permixon does not modulate the EDG-2 receptor.

20. Compound c also suppresses the proliferative effect of LPA on human synovial cells. Rheumatoid arthritis is characterized by uncontrolled proliferation of synovial tissue. Parada-Turska *et al.* (*Eur. J. Pharm.*, **2006**, *535*, 95) report that antirheumatic drugs inhibit proliferation synoviocytes *in vitro*. However, there is no evidence to suggest that this *in vitro* activity is predictive of *in vivo* efficacy at treating rheumatoid arthritis.

21. Compound c also suppresses the proliferative effect of LPA on human precursor fat cells. There is no evidence to suggest that this *in vitro* activity is predictive of *in vivo* efficacy at treating obesity.

22. The specification does not disclose evidence relevant to the treatment of any other chronic disease.

(8) the quantity of experimentation necessary

23. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if species of formulas I and III would be effective at treating chronic diseases including prostate hyperplasia, obesity and rheumatoid arthritis.

24. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claims 14, 15 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

26. The use of the term "acid group" in claims 14 and 20 renders the claim indefinite because the term does not describe a structure.

27. Claim 15 recites the limitation "wherein one or more selected from.." There is insufficient antecedent basis for this limitation in the claim.

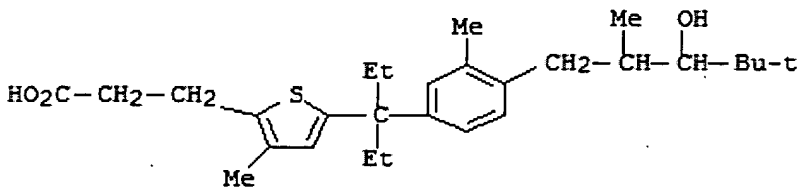
Claim Rejections - 35 USC § 102

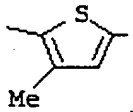
28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

29. Claims 9 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Shankar *et al.* (U.S. Publication No. 2004/0167132). Shankar *et al.* teach pharmaceutical compositions comprising EDG-2 antagonists for the treatment of diseases such as asthma (paragraph 0014) that can be used in combination with other EDG receptor antagonists (paragraph 0175).

30. Claims 9 and 20 are rejected under 35 U.S.C. 102 (e) as being anticipated by Dahnke *et al.* (WO 2003/101978). Dahnke *et al.* teach the compound



which is consistent with Formula III of claim 20 wherein Z^c is an acid group COOH, M^c is ethyl, E^c is a ring with a substituent 

, L^c is C with two ethyl substituents, D^c is phenyl with a methyl substituent, Q^c is CH_2, J^c is C, K^c is a bond, B^c is a methyl, T^c is a CH(OH), G^c is a bond, and R^c is a t-butyl (see Table 1, page 84, specifically Code 185 on page 90). The compounds taught by Dahnke *et al.* are intended for the treatment of chronic diseases such as osteoporosis and can be used in combination with estrogens and androgens (see page 147, lines 20-30).

31. Dahnke *et al.* do not teach that these compounds are EDG-2 antagonists. Because the chemical structure of the species taught by Dahnke *et al.* is identical to the claimed invention, there is a reasonable expectation that the species would meet this additional functional limitation. The discovery and characterization of properties of a known material do not make it novel (see MPEP § 2112). Furthermore, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP § 2112).

32. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01. Examiner cannot however determine whether or not the species taught by Dahnke *et al.* inherently possesses properties which anticipate or render obvious the claimed invention but

has basis for shifting the burden of proof to applicant as in In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). See MPEP § 2112.

Double Patenting

33. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
34. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
35. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

36. Claims 7, 9, 12, 14, 15 18 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 10/515,653. Although the conflicting claims are not identical, they are not patentably distinct from each other. Both sets of claims are drawn to compounds of formula I (see claim 1 of Application No. 10/515,653 and claims 12 and 18 of the instant application), which represent a sub-genus of formula III (claims 14 and 20 of the instant application). Claim 16 of Application No. 10/515,653 recites the use of compounds of formula I in combination with

other LPA receptor antagonists, an α1 blocking agent, an anticholinergic agent, a 5α-reductase inhibitor and/or an anti-androgenic agent to treat urinary system diseases. The urinary system diseases recited in the specification of Application No. 10/515,653 are chronic in nature. Therefore, claims 9, 18 and 20 are obvious over claim 16 of Application No. 10/515,653. Claim 12 of Application No. 10/515,653 is drawn to a method for treating a variety of diseases which are chronic in nature by administering the compounds of formula I. Therefore, claims 7, 12 and 14 are obvious over claim 12 of Application No. 10/515,653. Claim 15 of the instant application is obvious over claim 12 of Application No. 10/515,653 in view of claim 16. Note that the prohibition against double patenting rejections under 35 U.S.C. 121 does not apply in this case because Applicant voluntarily filed two or more applications without a restriction requirement by the examiner. See MPEP 804.01 A.

37. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

38. Claims 7, 9, 14, 15 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-80 of copending Application No. 10/530,249. Although the conflicting claims are not identical, they are not patentably distinct from each other. Both sets of claims are drawn to compounds of formula III (see claim 1 of Application No. 10/530,249 and claims 14 and 20 of the instant application). Claim 80 of Application No. 10/530,249 recites the use of compounds of formula III in combination with other LPA receptor antagonists, an α1 blocking agent, an anticholinergic agent, a 5α-reductase inhibitor and/or an anti-androgenic agent to treat urinary system diseases.

The urinary system diseases recited in the specification of Application No. 10/530,249 are chronic in nature. Therefore, claims 9 and 20 are obvious over claim 80 of Application No. 10/530,249. Claim 76 of Application No. 10/530,249 is drawn to a method for treating a variety of diseases which are chronic in nature by administering the compounds of formula III. Therefore, claims 7 and 14 are obvious over claim 76 of Application No. 10/530,249. Claim 15 of the instant application is obvious over claim 12 of Application No. 10/530,249 in view of claim 80. Note that the prohibition against double patenting rejections under 35 U.S.C. 121 does not apply in this case because Applicant voluntarily filed two or more applications without a restriction requirement by the examiner. See MPEP 804.01 A.

39. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

40. Claim 7 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9-24 of copending Application No. 10/483,815. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of Application No. 10/483,815 are drawn to methods for treating diseases comprising administering LPA receptor modulators. Claim 11 recites an LPA receptor antagonist for treating digestive organ diseases. Claim 12 recites examples of such diseases which are all chronic in nature. Claims 17 and 21 recite EDG-2 as the LPA receptor. Therefore claim 7 of the instant application is obvious over claims 11, 12, 17 and 21.

41. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

42. Claims 7, 10, 11 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8, 10-12, and 24-34 of copending Application No. 10/467,359. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 8 is drawn to a method for treating prostate hyperplasia comprising administering a LPA receptor antagonist. Claim 12 of Application No. 10/467,359 requires that the LPA receptor be EDG-2. Thus claims 7, 10 and 11 of the instant application are obvious over claims 8 and 12 of Application No. 10/467,359. Claim 15 of the instant application is obvious over claims 24-34 of Application No. 10/467,359 which recite other LPA receptor antagonists, an anticholinergic agent, a 5α-reductase inhibitor and/or an anti-androgenic agent for use in combination with the LPA receptor antagonists of claim 1.

43. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

44. Claims 7, 10, and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/477,106. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 6 of Application No. 10/477,106 is drawn to a subgenus of formula III of the instant application (see claim 14). Claim 16 of Application No. 10/477,106 is drawn to a method of treating a variety of chronic diseases including arteriosclerosis comprising administering the compounds of claim 6. Therefore claims 7, 10 and 14 are obvious over claims 6 and 16 of Application No. 10/477,106.

45. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

46. No claims are allowed.

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

48. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

49. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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